REMARKS

Applicants have cancelled claims 7, 13 and 18 without prejudice and have expressly reserved the right to pursue the full scope of the cancelled claim in subsequent continuation applications.

Applicants have added new claims 19-21. Support for these claims is found, e.g., in original claims 3, 5 and 6.

Applicants have amended claim 1 to describe the DNA probes of step b) with more particularity. Support for the amendment is found e.g. in paragraphs [0007]-[0009] wherein applicants have identified three genes where differences between sensitive and resistant strains occur in connection with the development of penicillin resistance and disclose that based on the finding of the differences between the penicillin-sensitive and penicillin-resistant strains applicant developed DNA probes by which the resistant and sensitive strains can be differentiated. Applicants further disclose probes that are sensitive-specific and probes that are resistant-specific for the penicillin binding protein genes PBP2x, PBP1a and PBP2b in penicillin sensitive or resistant strains.

Applicants have also amended claims 1 and 11 such that the step a) recites "isolating DNA from Streptococcus pneumoniae having unknown resistance to penicillin:"

Claims 1 and 6-10 stand rejected under 35 U.S.C. §112, first paragraph for purportedly lacking enablement. In view of the amendments to the claims and the following remarks Applicants request that the Examiner reconsider and withdraw the rejection of the claims.

Applicants have amended claim 1 to describe the DNA probes with more particularity. As amended the claimed method comprises hybridizing DNA isolated from a *S. pneumoniae* strain with at least two probes: The first probe specifically hybridizes to a DNA sequence that is specific to the penicillin binding protein genes of penicillin sensitive strains of *S. pneumoniae*, and the second probe specifically hybridizes to a DNA sequence that is specific to the penicillin binding protein gene of penicillin resistant strains. Support for this amendment is found in e.g. paragraphs [0007]-[0009]

> "[0007]...Three genes were identified where differences between sensitive and resistant strains occur in connection with the development of penicillin resistance: PBP2x, PBP1a and PBP2b.
>
> [0008]...A comparison between the DNA sequences shows within the genes regions which are present in all of the sensitive *S. pneumoniae* strains but are modified in resistant strains. ***
>
> [0009]...Because of the above finding that differences between penicillin-sensitive and penicillin-resistant strains occur within certain genes, the applicant developed DNA probes by means of which resistant and sensitive strains can be differentiated. In this connection, reference is made to FIG. 4. The probes which are specific to sensitive sequences discriminate genes which code for low-affinity PBP variants responsible for penicillin resistance. The probes which are specific to resistant sequences react with a very frequently occurring class of PBP variants and can also be used for epidemiological purposes.

Based upon this teaching, one of skill in the art, without undue experimentation, could make and use the probes that specifically hybridize to DNA sequences that are specific to the PBP genes of sensitive strains or specific to the PBP genes of resistant strains as set forth in the claims.

> "A decision on the issue of enablement required determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation. It is not fatal if some experimentation is needed, for the patent document is not intended to be a production specification."
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> *Northern Telecom, In. v. Datapoint Corp.*, 15 USPQ 1321, 1229

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 190 USPQ 214 (CCPA 1976). And the question of how much experimentation is "undue" in each case must be determined on its own facts. In the present application, Applicants have taught those of skill in the art to compare the sequences of the penicillin binding protein genes (particularly PBP2x, PBP1a and PBP2b) of penicillin sensitive and resistant strains of *S. pneumoniae* to identify sequences that are particular to either the sensitive or resistant strains, and to prepare DNA probes based upon those particular sequences. Applicants have provided examples of "sensitivity-specific" and "resistance-specific" probes for the three PBPs recited in the claims, i.e., probes that have sequences that are common to the PBPs of sensitive strains but modified in resistant strains, and probes that have sequences that occur frequently in the PBP variants of resistant strains (last sentence paragraph [0009]). Applicants' claimed method also comprises determining whether or not the *Streptococcus pneumoniae* is sensitive to penicillin by detecting which probes hybridize to the isolated DNA. Such determinations do not require ingenuity beyond that expected of one of ordinary skill in the art. The science of hybridization is well-known to those of skill in the art and oligonucleotide hybridization techniques have been employed routinely for decades for detecting and distinguishing particular DNA sequences. Those of skill in the art routinely adjust hybridization conditions to detect specific hybridizations because they appreciate the factors that affect oligonucleotide hybridization, e.g., AT/GC content as well as hybridization conditions. Such adjustments require no more than routine calculations. Thus

the skilled artisan would readily perform trial runs of appropriate hybridization conditions in which their selected probes would specifically hybridize to their complementary sequence in the isolated *Streptococcus pneumoniae* DNA, to distinguish the PBP sequences of penicillin sensitive and resistant strains. Applicants have provided an example of an oligonucleotide array demonstrating specific hybridization of particular probes to the *Streptococcus pneumoniae* DNA (see e.g., Fig. 2). Thus, one of skill in the art could readily reproduce Applicants' method for other "sensitivity-specific" and "resistance-specific" probes derived from the three PBPs based on Applicants' disclosure without undue experimentation, and as such Applicants have enabled the current claims.

In view of the foregoing remarks and amendments to the claims, Applicants request that the Examiner reconsider and withdraw the rejection of claims 1 and 6-10 under 35 U.S.C. 112, first paragraph for purported lack of enablement.

Claims 7 stands rejected under 35 U.S.C. 112, second paragraph for purportedly being indefinite. Although Applicants respectfully disagree, Applicants have cancelled claim 7 without prejudice and have thus obviated the rejection under 35 U.S.C. 112, second paragraph.

Claims 1 and 6 stand rejected under 35 U.S.C. §102(b) for purportedly being anticipated by Dowson et al. PNAS (1990) 87:5858-5662 ("Dowson et al."). Applicants respectfully disagree. Dowson et al. does not teach determining whether a *Streptococcus pneumoniae* of unknown resistance is sensitive or resistant to penicillin by detecting which probe or probes hybridize to its isolated DNA.

> Anticipation under 35 U.S.C. §102 requires the disclosure in a single piece of prior art of each and every limitation of a claimed invention.
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> *Electro Med. Sys. S.A. v. Cooper Life Sciences*, 32 USPQ2d 1017, 1019 (Fed. Cir. 1994).

Applicants claimed method for testing *Streptococcus pneumoniae* for resistance to penicillin comprises isolating DNA from a *Streptococcus pneumoniae* strain having unknown resistance to penicillin. Dowson et al. is attempting to determine whether known penicillin resistant strains of viridian streptococci isolated in the U.K. emerged by the horizontal transfer of altered PBP genes from penicillin-resistant strains of *S. p neumoniae* into penicillin-sensitive strains of viridins streptococci. Dowson et al. hybridizes "resistance block" probes to DNA isolated from various streptococci of known resistance in an attempt to determine the source of the "resistant blocks" (see page 5859, right col. and page 5862 left col. last paragraph). Thus, Dowson et al. in contrast to Applicants, only uses strains of streptococci having known resistance to penicillin. As such, Dowson et al. does not teach each and every limitation of the claimed invention and therefore does not anticipate the invention as claimed.

In view of the foregoing remarks and amendments to the claims, Applicants request that the Examiner reconsider and withdraw the rejection of Claims 1 and 6 under 35 U.S.C. §102(b) for purportedly being anticipated by Dowson et al

Claims 2, 3, 11, 12 and 14 stand rejected under 35 U.S.C. §103(a) for purportedly being unpatentable over Dowson et al. and further in view of Kell et al. (*Infection and Immunity* 61(10):4382-4391 (1993))("Kell et al."). Applicants respectfully disagree.

As discussed above, Dowson et al. disclose their attempt to determine the source of the "resistant blocks" of nucleotide sequence in various resistance genes in streptococci of known penicillin resistance. On page 5859, right col. second

full paragraph, Dowson et al. discloses the use of probes from regions of class A and class B PBP2B that differ extensively from each other and from the PBP2B genes of penicillin-sensitive strains. Dowson et al. discloses that this region is altered in all penicillin resistant pneumococci and that oligonucleotides from these "resistant blocks" were used as probes to search the DNA of penicillin resistant viridins streptococci for class A or class B PBP2B genes. Dowson et al. also discloses the use of a 1.5kb fragment from a penicillin-sensitive *S. pneumoniae* as a probe, but this probe was not hybridized to *S. pneumoniae* DNA: Rather this 1.5kb probe was hybridized only to *S. sanguis* and *S. oralis* DNA. From the inability of the 1.5kb probe to hybridize to penicillin sensitive *S. sanguis* and weak hybridization to penicillin-sensitive *S. oralis*, Dowson et al. concluded that *S. sanguis* and *S. oralis* diverged considerably from *S. pnuemoniae* (page 5859, right col. third full paragraph). Thus Dowson was not hybridizing two different probes, one a penicillin sensitive probe and another penicillin resistant probe, to the DNA of *S. pneumoniae* of unknown resistance, but rather was assaying known penicillin resistant viridins streptococci for related resistance sequences.

The combination of Dowson et al. with Kell et al. entitled "Molecular Epidemiology of Penicillin-Resistant Pneumococci Isolated in Nairobi, Kenya" also fails to render the claimed invention obvious. As the title indicates, Kell et al. is directed to an epidemiologic analysis of pneumococci strains that were known to be penicillin resistant. In particular, Kell et al. uses gene fingerprinting and DNA sequencing to distinguish the penicillin-binding protein genes in 23 penicillin resistant isolates. See e.g., the first sentence of the abstract and page 4383, "Materials and Methods" right col. section entitled "PBP gene fingerprinting" where Kell et al. discloses, that the amplified fragments were gel purified, digested with restriction enzymes, end labeled, fractionated on a gel and then autoradiographed to produce gene fingerprints, and also see page 4384 which states "the regions of the PBP genes that were sequenced were those

that were the most variable in unrelated penicillin-resistant pneumococci." (emphasis added)

The Examiner states that Kell et al. teach a sequence that is 100% identical to SEQ ID NO: 8 (Office Action page 10). However, all the strains Kell et al. analyzes were initially selected because they were known to be penicillin resistant. Therefore, Kell et al. does not teach distinguishing between pneumococci that are resistant and susceptible to penicillin by using a probe of SEQ ID NO: 8 or any other sequence. Thus Kell et al. does not provide the motivation to develop a method to test *S. pneumoniae* for penicillin resistance and fails to provide the motivation to use *any* probe to distinguish between penicillin resistant and sensitive strains. As such, Kell et al. in combination with Dowson et al. fails to teach or suggest the claimed method for testing a *S. pneumoniae* for resistance to penicillin.

Furthermore, regarding claim 11, the claimed method requires the use of two DNA probes wherein the sequence of the probes is selected from particular Markush groups of nucleotide sequences. Neither Dowson et al. or Kell et al. teach or suggest combining two probes having the particular sequences recited in this claim in a method such as that presently claimed. Thus Dowson et al. combined with Kell et al. fails to render the method as claimed obvious. Applicants believe claim 11 and the claims that depend on claim 11 are in condition for allowance.

In view of the forgoing remarks and amendments to the claims, Applicants request that the Examiner reconsider and withdraw the rejection of claims 2, 3, 11, 12 and 14 under 35 U.S.C. 103(a).

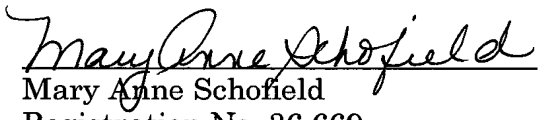
Claim 18 stands rejected under 35 U.S.C. first paragraph for purportedly lacking enablement. Although Applicants respectfully disagree, Applicants have cancelled claim 18 without prejudice and thus have obviated the rejection.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #99380.B270037).

Respectfully submitted,

MAY 14, 2008



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